Pneumocystis jirovecii pneumonia in renal transplant recipients occurring after discontinuation of prophylaxis: a case–control study

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Abstract

A case–control study was conducted to identify risk factors for *Pneumocystis jirovecii* pneumonia (PCP) in renal transplant recipients. Eleven cases of PCP were matched with 22 controls. Cases occurred a median of 18 months after transplantation, and none of the recipients was receiving prophylaxis. Univariate analysis showed that graft rejection, duration of steroid use, use of mammalian target of rapamycin (mTOR) inhibitors and lymphocytopenia at the time of prophylaxis discontinuation were risk factors for PCP. In the multivariate model, only graft rejection (OR 8.66, p 0.017) remained significantly associated with PCP. In patients with a history of graft rejection, PCP prophylaxis should be maintained, especially among those with lymphocytopenia.

Keywords: Lymphocyte count, *Pneumocystis jirovecii*, prophylaxis, renal transplantation

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Several recent studies have described clusters of renal transplant recipients diagnosed with *Pneumocystis jirovecii* pneumonia (PCP) several months after transplantation and prophylaxis discontinuation [1–8]. A history of graft rejection has been identified as a potential risk factor in several studies, and the role of immunosuppressive regimens has also been debated [4–8]. Interpatient transmission of *P. jirovecii* or prophylaxis failure was suspected in some studies [9,11].

Following the occurrence of consecutive cases of PCP among renal transplant recipients in our centre, we decided to perform a retrospective case–control study to identify risk factors associated with PCP. The study was performed in a single renal transplant unit in Paris, where PCP prophylaxis with cotrimoxazole (480 mg once daily) is started after transplantation for a fixed duration of 3 months.

Cases were defined by the identification in bronchoalveolar lavage fluid or in induced sputum of *P. jirovecii* trophozoites or cysts (by Giemsa staining and/or immunofluorescence) or detection of *P. jirovecii* DNA by PCR in cases with clinical and radiological features consistent with PCP and no other plausible diagnosis. Using our computerized database, each case was matched with two controls without PCP at the date of renal transplantation; cases and controls therefore had similar durations of follow-up. Univariate and multivariate analyses were then performed, using exact conditional logistic regression, in order to identify risk factors associated with PCP. Associations of variables with PCP were expressed in terms of exact ORs with their 95% CIs. Reported p-values are mid-p-values that adjusted for the discreteness of the distribution. All tests were two-sided, and p-values of <0.05 were taken to indicate statistical significance. Analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

From January 2006 to June 2007, 11 cases of PCP were diagnosed among 11 patients who underwent renal transplantation between June 1992 and February 2006. During this period, 750 patients underwent renal transplantation in our centre. The characteristics and outcome of PCP cases are reported in Table 1. All cases occurred late after PCP prophylaxis withdrawal, a median of 18 months after renal transplantation. All required hospital admission and presented with the usual features of PCP. It is of note that five patients (45%) presented with acute respiratory failure. The outcome was satisfactory after patients received high-dose cotrimoxazole therapy, except for two patients, one of whom died. This unusually low mortality rate might be related to the small sample size of our study or to the early diagnosis of PCP in our institution, which has a great deal of experience in PCP

TABLE 1. Characteristics and outcome of 11 cases of *Pneumocystis jirovecii* pneumonia (PCP) among renal transplant recipients

Cases	*n* = 11
Median age, years (range)	53 (28–73)
Male sex, *n* (%)	7 (64)
Median time between PCP and transplantation, months (Q_1–Q_3)[a]	18 (15–96)
Proportion of patients still under prophylaxis at PCP diagnosis, *n* (%)	0 (0)
Clinical presentation	
Cough, *n* (%)	11 (100)
Fever, *n* (%)	11 (100)
Dyspnoea, *n* (%)	8 (73)
Acute respiratory failure, *n* (%)	5 (45)
Lymphocyte count at prophylaxis discontinuation, median (Q_1–Q_3)/μL	430 (348–688)
Lymphocyte count at PCP diagnosis, median (Q_1–Q_3)/μL	440 (380–540)
PCP diagnosis, *n* (%)	
P. jirovecii cysts in BAL fluid or induced sputum	10 (91)
P. jirovecii DNA detected by PCR in induced sputum[b]	1 (9)
Post-transplant CMV viraemia, *n* (%)	8 (73)
Bacterial co-infection at PCP diagnosis, *n* (%)	4 (36)
Pulmonary[c]	3 (27)
Bacteraemia (*Listeria monocytogenes*)	1 (9)
Radiological findings on chest X-ray or CT scan, *n* (%)	
Bilateral alveolar or interstitial infiltrates	11 (100)
Fibrosis	1 (9)
Treatment	
Cotrimoxazole, *n* (%)	11 (100)
Outcome, *n* (%)	
Cure	9 (81)
Chronic respiratory failure	1 (9)
Death	1 (9)

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CT, computed tomography.
[a](Q_1–Q_3): interquartile range.
[b]This patient had clinical and radiological manifestations consistent with PCP, and there was no alternative diagnosis. He could not undergo BAL, because of respiratory failure. He fully recovered after PCP treatment.
[c]BAL cultures were positive for *Streptococcus pneumoniae* in one patient, for *Staphylococcus aureus* and *Pseudomonas aeruginosa* in one patient, and for *P. aeruginosa* in one patient.

diagnosis and treatment, and where many human immunodeficiency virus-infected patients are taken care of.

In the case–control study, a number of variables were associated with the risk of PCP in the univariate analysis (Table 2). Indeed, and similar to what has been reported previously, a history of graft rejection was one of the strongest predictors of PCP, with an OR of 14.4 (95% CI 2.1–inf, p 0.002) [4,5,7]. Also, the use of mTOR inhibitors (OR 7.7, 95% CI 1.2–inf, p 0.02) and a longer duration of high-dose steroid use (OR 1.6 per month, 95% CI: 1.04–2.93, p 0.005) were both associated with a higher risk of PCP. Cases were, however, less likely than controls to have received calcineurin inhibitors (OR 0.09, 95% CI 0–0.67, p 0.004). Finally, a low lymphocyte count (<500/μL) at the time of prophylaxis discontinuation was associated with a higher risk of PCP (OR 18.1, 95% CI 1.66–inf, p 0.0027). We could not assess CD4 T-cell counts in this study, as they were not routinely measured in our patients.

Given the low number of cases in this study, and because variables associated with the risk of PCP in the univariate model were likely to be colinear with rejection, we tested, in a multivariate model, whether a low lymphocyte count (<500/μL) at the time of prophylaxis discontinuation remained associated with PCP when graft rejection was selected as the main variable. In this model, only graft rejection (OR 8.66, p 0.017) remained significantly associated with PCP, whereas a low lymphocyte count was no longer significantly associated with the risk of PCP, although a trend was seen (OR 5.84, p 0.083) (Table 2). Indeed, a low CD4 T-cell count has previously been suggested to be a very reliable risk factor for PCP in patients with and without human immunodeficiency virus infection [11–13]. In renal transplant recipients, as monitoring of CD4 T-cell counts is not routinely performed, total lymphocyte count could be a good surrogate marker and a proxy of immunosuppression resulting from use of steroids and immunosuppressive agents. It is also a simple and convenient marker to measure. Owing to the small sample size in our study, however, and on the basis of the experience of a single institution, it may not be possible to generalize our findings to other renal transplant centres, and further studies need to be conducted, in particular to confirm the role of lymphocytopenia.

Despite its limitations, our study therefore suggests that among patients with graft rejection, PCP prophylaxis should be maintained or resumed, especially in patients with low lymphocyte counts (<500/μL). Indeed, all cases of PCP in our study were reported among patients in whom PCP prophylaxis had been discontinued. PCP prophylaxis has been very successful in almost eliminating the risk of PCP among renal transplant recipients during the first 3 months after transplantation. PCP prophylaxis usually relies on the use of a low daily dose of cotrimoxazole. Renal intolerance is unusual when such a low dose of cotrimoxazole is used, even in renal transplant recipients, and is fully reversible upon treatment discontinuation. In cases of sulfonamide intolerance, oral atovaquone (750 mg twice daily) appears to be a simple and safe alternative, with a low risk of drug–drug interactions and no renal toxicity [1].

In conclusion, among renal transplant recipients, PCP can still occur several months after transplantation, late after prophylaxis discontinuation. Graft rejection appears to be the major risk factor for PCP in these patients. PCP prophylaxis should therefore be maintained or resumed, especially when lymphocytopenia is present, as it could further increase the risk of PCP.

Transparency Declaration

All authors declare no conflict of interest.

TABLE 2. Univariate and multivariate analyses of risk factors for *Pneumocystis jirovecii* pneumonia (PCP) among renal transplant recipients

			Univariate analysis		Multivariate analysis	
	Cases	Controls	OR (95% CI)	Mid-p-value	OR (95% CI)	Mid-p-value
No. of patients	11	22				
Male gender, *n* (%)	7 (64)	15 (68)	0.81 (0.13–5.87)	0.85	–	–
Age at transplant (years), mean (SD)	47 (15)	43 (14)	1.03 (0.97–1.12)	0.35	–	–
Dialysis duration (years), median (Q_1–Q_3)[a]	5 (4–7)	4 (2–7)	1.12 (0.90–1.44)	0.32	–	–
Transplantation number (%)						
1	9 (82)	17 (77)	1	Ref.	–	–
≥2	2 (18)	5 (23)	0.77 (0.07–5.76)	0.84	–	–
Induction of immunosuppressive treatment, *n* (%)						
None	0 (0)	1 (5)	1	Ref.	–	–
ATG	7 (64)	17 (77)				
IL-2RA	4 (36)	4 (18)	0.21 (0.004–2.84)	0.20	–	–
Transplant rejection episodes, *n* (%)						
0	2 (18)	17 (77)	1	Ref.	–	–
≥1	9 (82)	5 (23)	14.4 (2.1–Inf)	0.002	8.66 (1.17–Inf)	0.017
Corticosteroids after rejection, *n* (%)	8 (73)	5 (23)	11.5 (1.66–Inf)	0.004	–	–
OKT3 after rejection, *n* (%)	1 (9)	1 (5)	0.50 (0.01–Inf)	0.67		
Maintenance immunosuppressive treatment, *n* (%)[b]						
Antiproliferative drugs	8 (73)	19 (86)	0.42 (0.03–3.97)	0.52		
Calcineurin inhibitors	6 (55)	21 (95)	0.09 (0–0.67)	0.004		
mTOR inhibitors	3 (27)	0 (0)	7.70 (1.02–Inf)	0.019		
Corticosteroids	9 (82)	16 (73)	2.00 (0.05–Inf)	0.17		
Duration of treatment by corticosteroids (months), >0.25 mg/kg per day, median (Q_1–Q_3)	3 (2–7)	1.5 (0.3–3)	1.60 (1.04–2.93) per month	0.005		
Lymphocyte count <500/μL at prophylaxis discontinuation, *n* (%)	7 (64)	4 (18)	18.1 (1.66–Inf)	0.0027	5.84 (0.69–Inf)	0.083
History of CMV viraemia	8 (73)	11 (50)	2.63 (0.56–Inf)	0.15		

ATG, antithymocyte globulins; CMV, cytomegalovirus; IL-2RA, IL-2 receptor antagonist; Inf, infinity; mTOR, mammalian target of rapamycin; SD, standard deviation.
Associations of variables with PCP are expressed in terms of exact ORs with their 95% CIs. Reported p-values are mid-p-values that adjust for the discreteness of the distribution.
[a]Q_1–Q_3, interquartile range.
[b]Patients received more than one immunosuppressive drug, so the total is more than 100%.
Antiproliferative drugs were mycofenolate mofetil or azathioprine; calcineurin inhibitors were cyclosporine or tacrolimus; mTOR inhibitors were sirolimus or everolimus.

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